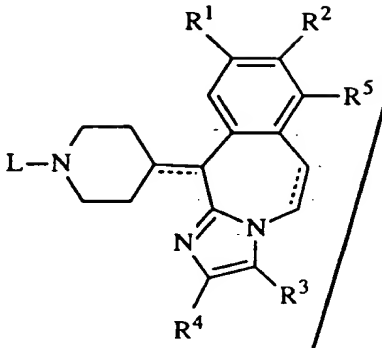
Claims

1. A compound having the formula



(I),

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond,

R^1 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy, hydroxycarbonyl-C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, aminocarbonyl or phenyl substituted with C_{1-4}alkyloxycarbonyl or hydroxycarbonyl; or,

L represents a radical of formula

-Alk-Y-Het^1 (a-1),

-Alk-NH-CO-Het^2 (a-2) or

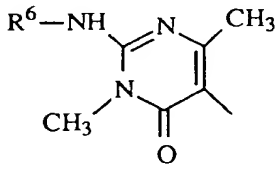
-Alk-Het^3 (a-3); wherein

Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

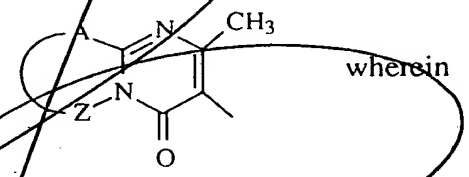
Het^1, Het^2 and Het^3 each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC_{1-4}alkyl, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl or one or two C_{1-4}alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and

Het^3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



(b-1)

or



(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

A-Z represents -S-CH=CH-, -S-CH_2-CH_2-, -S-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH_2-CH_2-CH_2-CH_2-, -N(CH_3)-C(CH_3)=CH- or -CH=C(CH_3)-O-;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine is ecxluded.

2. A compound according to claim 1 wherein L is C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl.

3. A compound according to claim 1 wherein

R^3 represents hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-4}alkyl or hydroxycarbonyl;

R^4 represents hydrogen, halo or hydroxyC_{1-4}alkyl; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylaminoC_{1-4}alkyl, aryl-C_{1-4}alkyl, propenyl, or

L is a radical of formula (a-1), (a-2) or (a-3), wherein

Het^1, Het^2, and Het^3 each represent furanyl, oxazolyl or thiazolyl each optionally substituted with C_{1-4}alkyl; thiadiazolyl optionally substituted with amino, pyridinyl; or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and

Het^3 may also represent a radical of formula (b-2).

4. A compound according to claim 3 wherein

R^1 represents hydrogen or halo;
R^2 represents hydrogen, halo or C_{1-4}alkyloxy; and
L represents ~~hydrogen,~~ C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, or a radical of formula (a-1), wherein Y represents NH.

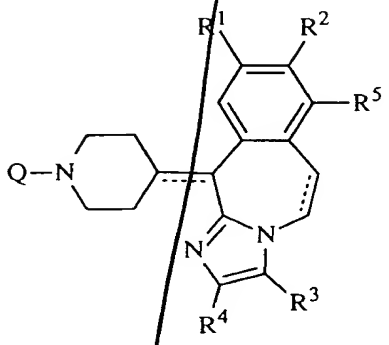
5. A compound according to claim ~~1~~ wherein said compound is selected from the group consisting of
5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;
9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;
11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine;
6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-methanol;
8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine;
6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde;
6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid;
7-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine; and
4-(8-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-propanoic acid dihydrate.

6. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

7. A method of preparing a pharmaceutical composition as claimed in claim 6, characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 is intimately mixed with a pharmaceutical carrier.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

9. A compound having the formula



(VII),

an acid addition salt thereof or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond,

R^1 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

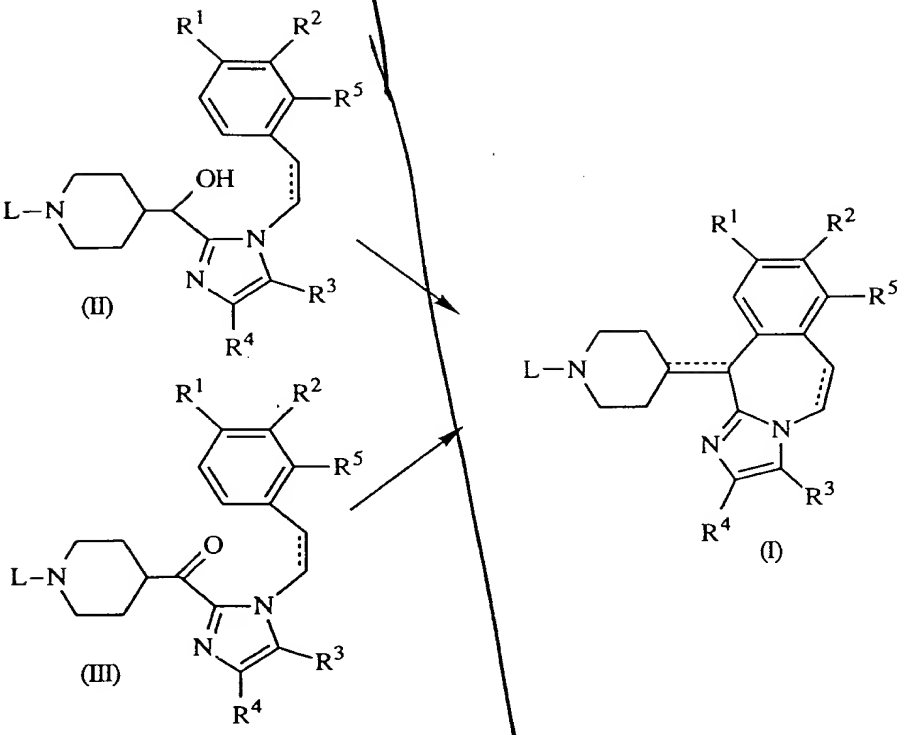
R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)-aminothiocarbonylamino, $(CH_3O)_2CH\text{-}CH_2\text{-}NH\text{-}C(=NCH_3)\text{-}NH$- or methylsulfonyloxy; provided that 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3]-benzazepine-11-ylidene)piperidine is excluded.

10. A process for preparing a compound as defined in any one of claims 1 to 5, characterized by

a) cyclizing an alcohol of formula (II) or a ketone of formula (III) in the presence of an acid;

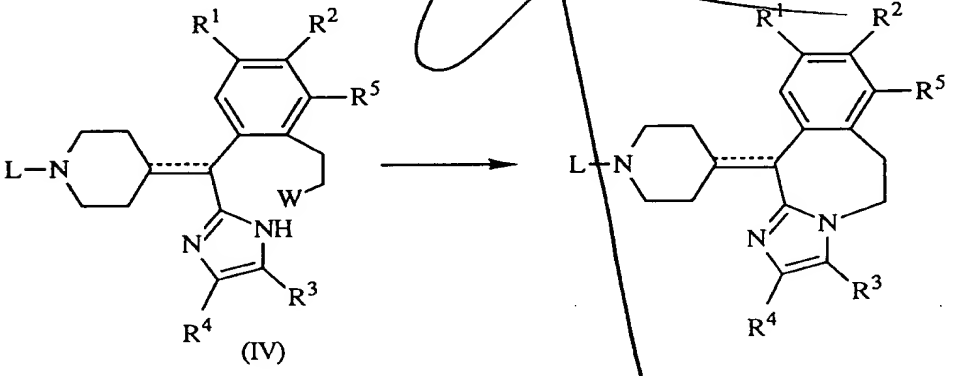


(II)

(III)

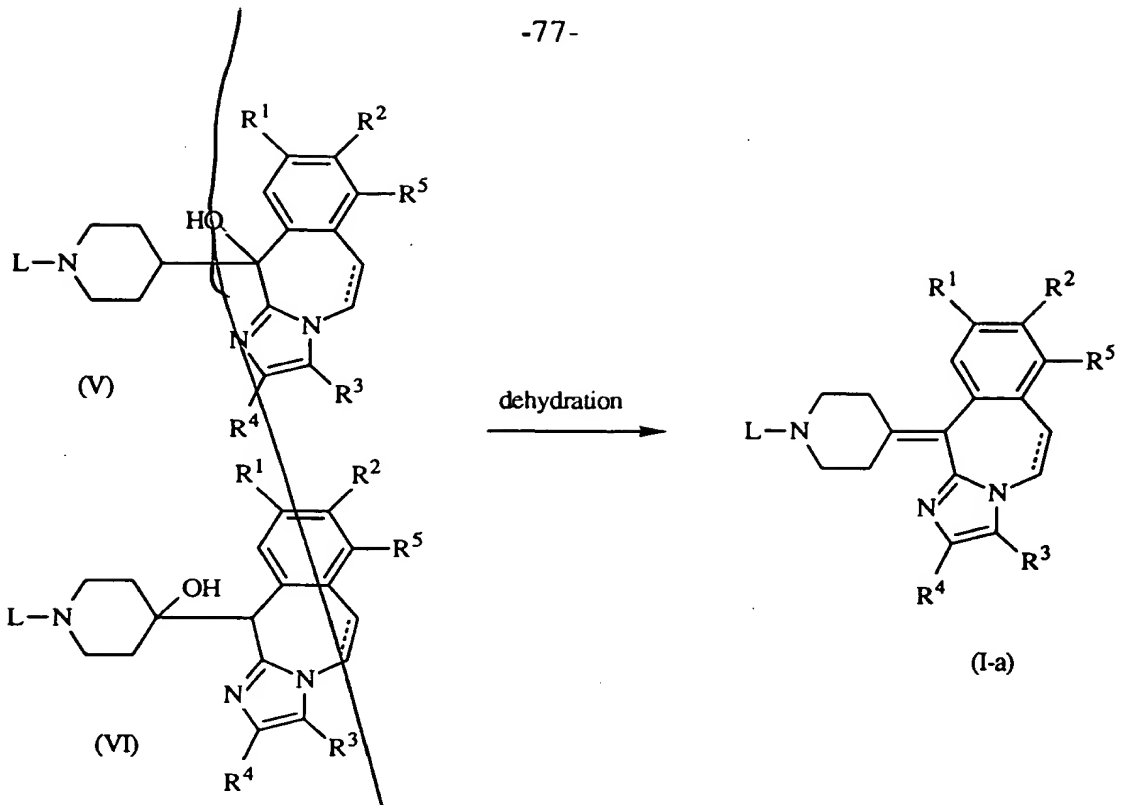
(I)

b) cyclizing an intermediate of formula (IV) wherein W represents a reactive leaving group, thus yielding a compound of formula (I) wherein the central ring of the tricyclic moiety does not contain an optional bond;

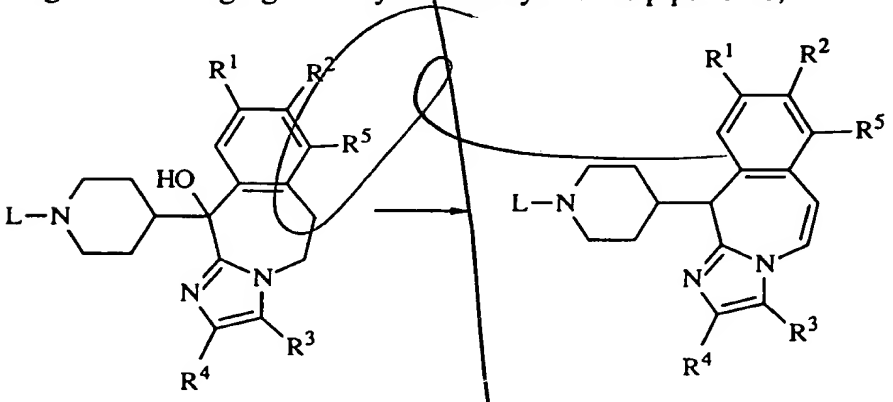


(IV)

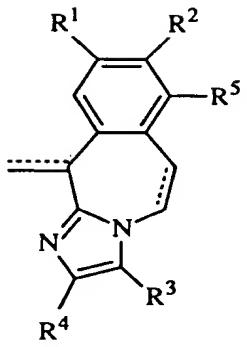
c) dehydrating an alcohol of formula (V) or (VI) in the presence of a dehydrating reagent, thus yielding a compound of formula (I) wherein a double bond exists between the piperidinyl and the tricyclic moiety;



d) dehydrating an alcohol of formula (V) wherein the central ring of the tricyclic moiety does not contain an optional bond, in the presence of a dehydrating reagent, thus yielding a compound of formula (I) with a double bond in the tricyclic moiety and a single bond bridging the tricyclic moiety and the piperidine;

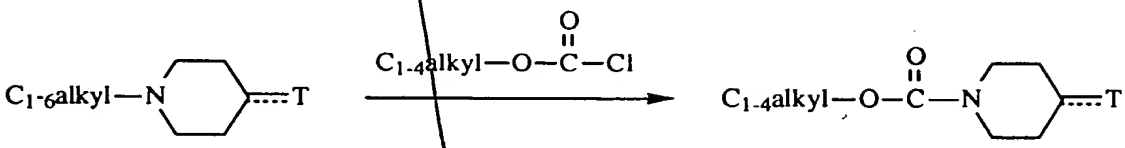


e) reacting an intermediate of formula (I-b) wherein ----T represents an imidazo[2,1-b]-[3]benzazepine moiety of formula



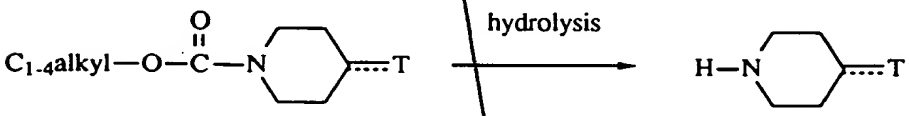
=

with C_{1-4}alkylchloroformate in the presence of a base and in a reaction-inert solvent yielding a compound of formula (VII-a)



(I-b) (VII-a)

which can be hydrolyzed to a compound of formula (I-c)

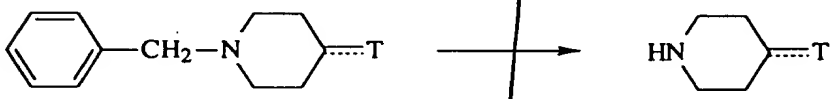


(VII-a) (I-c)

in the presence of an acid or a base;

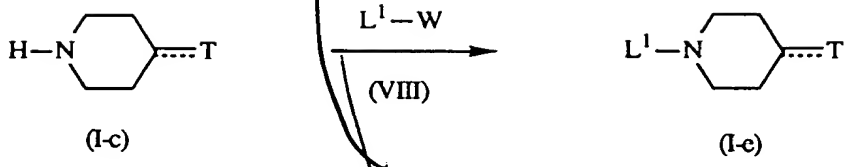
f) reacting a compound of formula (I-b) with an ~~α-halo-C_{1-4}alkyl~~ chloroformate in a reaction-inert solvent yielding a compound of formula (I-c);

g) debenzylating a compound of formula (I-d) by catalytic hydrogenation in the presence of hydrogen and a catalyst in a reaction-inert solvent;



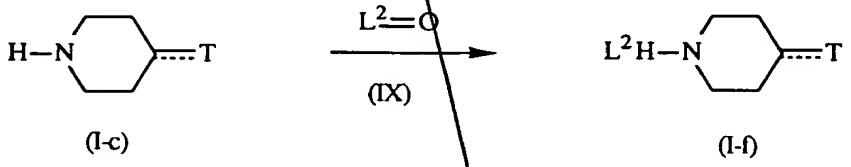
(I-d) (I-c)

h) N-alkylating a compound of formula (I-c) with a reagent of formula (VIII) in a reaction-inert solvent, optionally in the presence of a base;



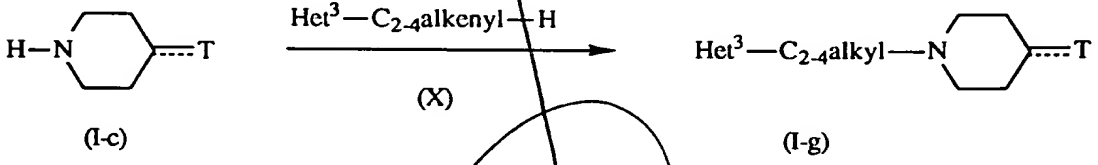
(I-c) (I-c)

i) reductively N-alkylating a compound of formula (I-c) with a reagent of formula $L^2=O$ (IX) wherein L^2 represents a geminal bivalent C_{1-6}alkylidene radical which optionally may be substituted, in a reaction-inert solvent, in the presence of a base;



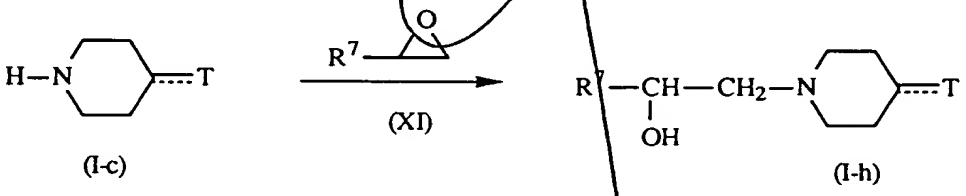
(I-c) (I-f)

j) reacting a compound of formula (I-c) with a reagent of formula (X) in a reaction-inert solvent;



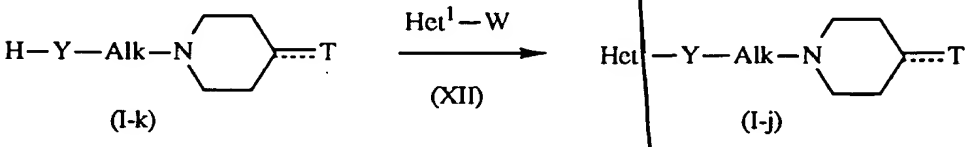
(I-c) (I-g)

k) reacting a compound of formula (I-c) with an epoxide of formula (XI) wherein R^7 represents hydrogen, C_{1-4}alkyl or aryloxyC_{1-4}alkyl in a reaction-inert solvent;



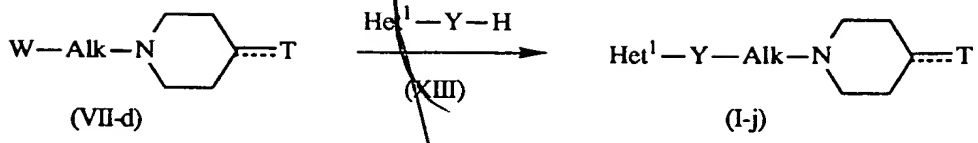
(I-c) (I-h)

l) reacting a compound of formula (I-k) with a reagent of formula (XII) in a reaction-inert solvent in the presence of a base;



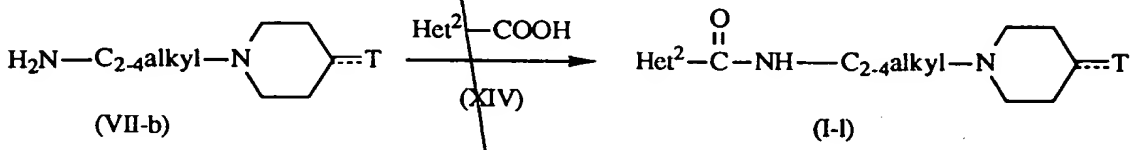
(I-k) (I-j)

m) reacting a compound of formula (VII-d) with a reagent of formula (XIII) in a reaction-inert solvent in the presence of a base;



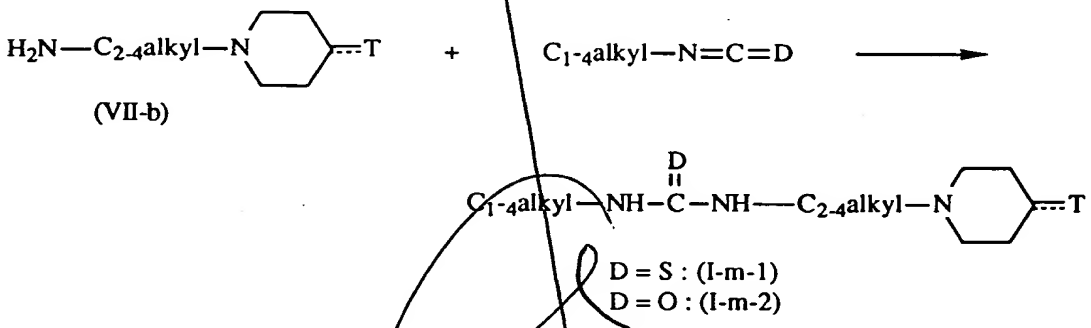
(VII-d) (I-j)

n) N-acylating a compound of formula (VII-b) with a carboxylic acid of formula (XIV) in a reaction-inert solvent;

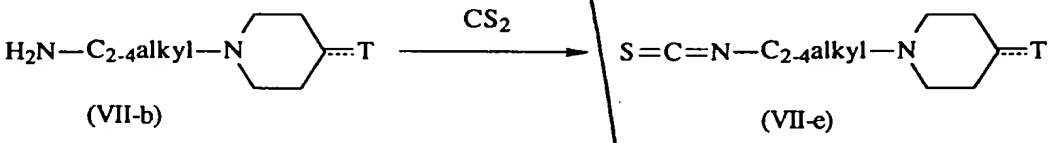


(VII-b) (I-l)

o) reacting a compound of formula (VII-b) with a C_{1-4}alkyliso(thio)cyanate in a reaction-inert solvent;

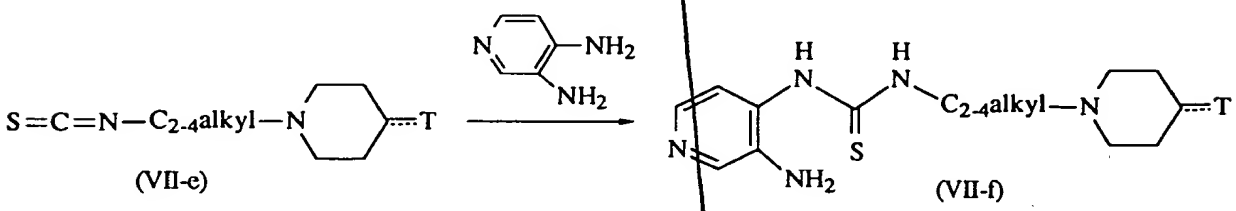


p) reacting a compound of formula (VII-b) with carbon disulfide in the presence of a dehydrating reagent yielding a compound of formula (VII-e)



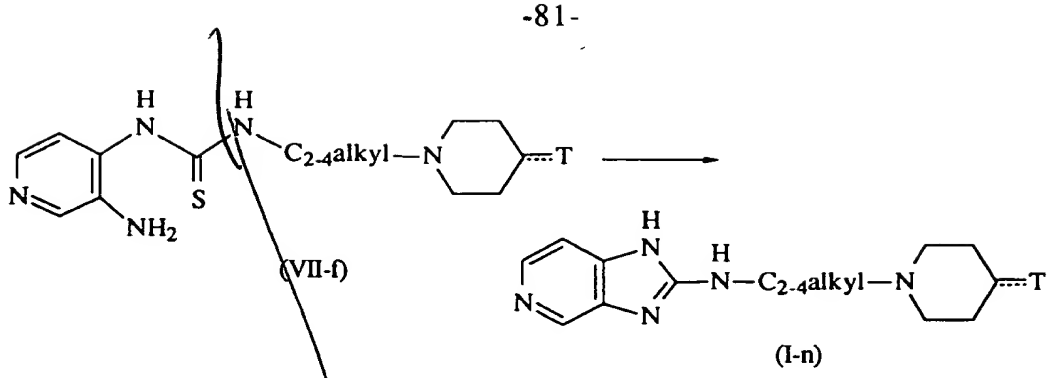
(VII-b) (VII-e)

which can be reacted with 3,4-diaminopyridine in a reaction-inert solvent, thus yielding a compound of formula (VII-f)



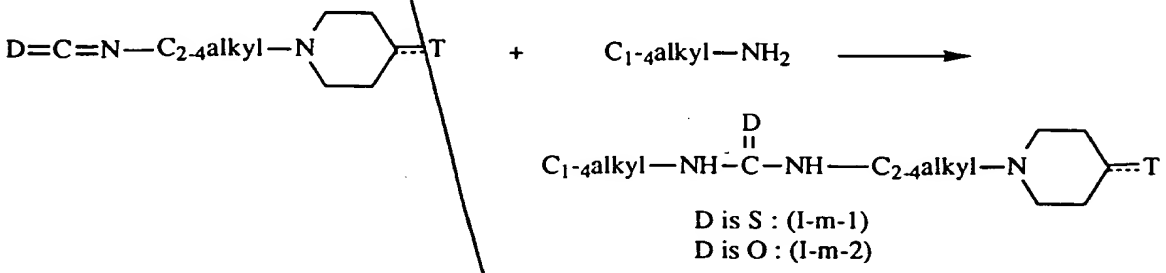
(VII-e) (VII-f)

which can be cyclized with a metal oxide into a compound of formula (I-n);



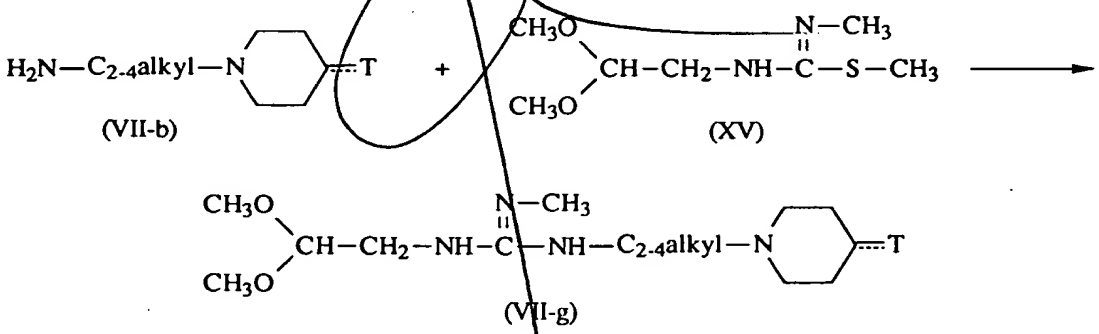
(VII-f) (I-n)

q) reacting a compound of formula (VII-e) or the corresponding isocyanate with C_{1-4}alkylamine in a reaction-inert solvent;



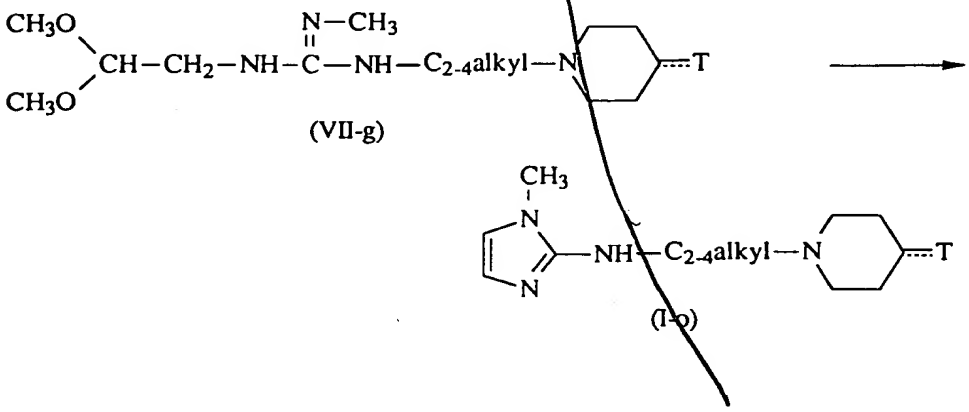
D is S : (I-m-1)
D is O : (I-m-2)

r) reacting a compound of formula (VII-b) with a reagent of formula (XV) in a reaction-inert solvent yielding a compound of formula (VII-g)



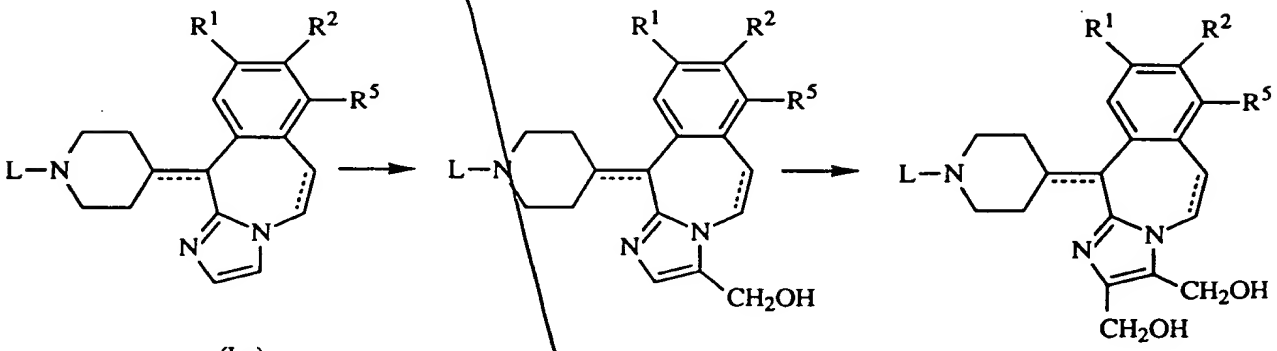
(VII-b) (XV) (VII-g)

which can be cyclized in an acidic aqueous solution into a compound of formula (I-o);



(VII-g) (I-o)

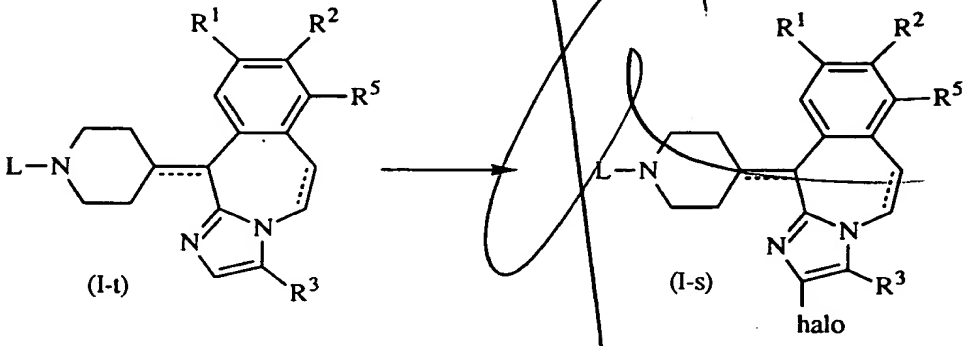
s) reacting a compound of formula (I-p) with formaldehyde optionally in the presence of a carboxylic acid-carboxylate mixture



(I-p) (I-q) (I-r)

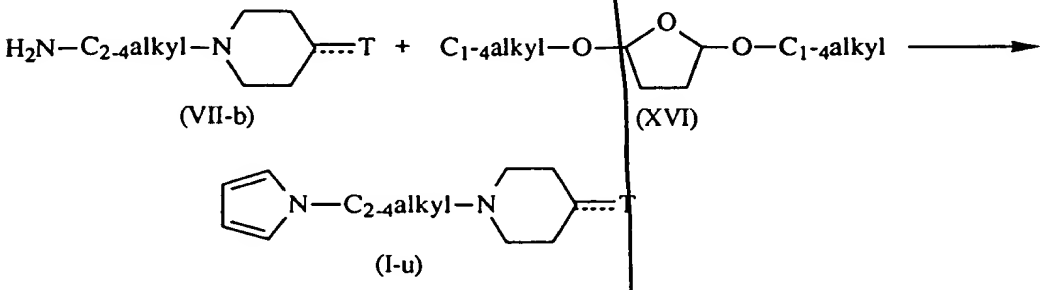
and optionally further oxidizing the compound (I-q) and (I-r) to the corresponding aldehyde or carboxylic acid;

t) halogenating a compound of formula (I-t) in the presence of a halogenating reagent;



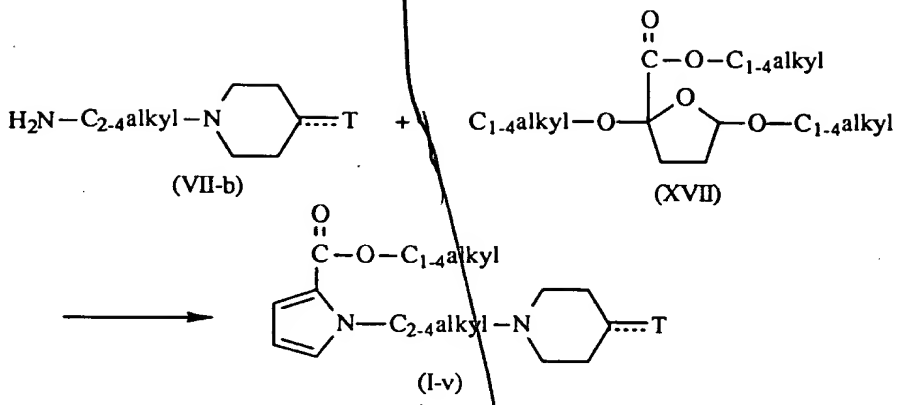
(I-t) (I-s)

u) reacting a compound of formula (VII-b) with a reagent of formula (XVI) in the presence of an acid;



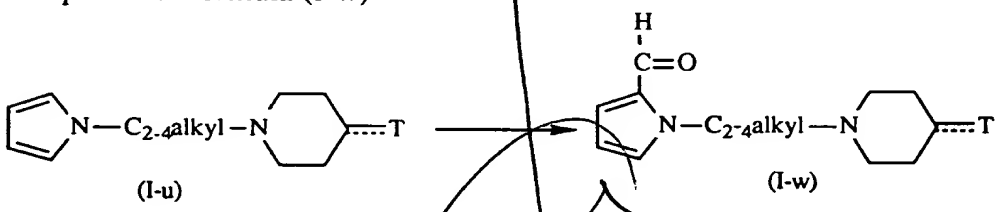
(VII-b) (XVI) (I-u)

v) reacting a compound of formula (VII-b) with a reagent of formula (XVII) in the presence of an acid yielding a compound of formula (I-v)

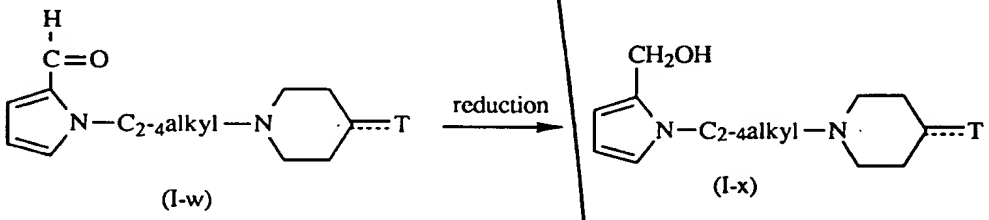


which optionally can be hydrolyzed in the corresponding 2-hydroxycarbonyl-1-pyridyl compound in the presence of an acid or a base;

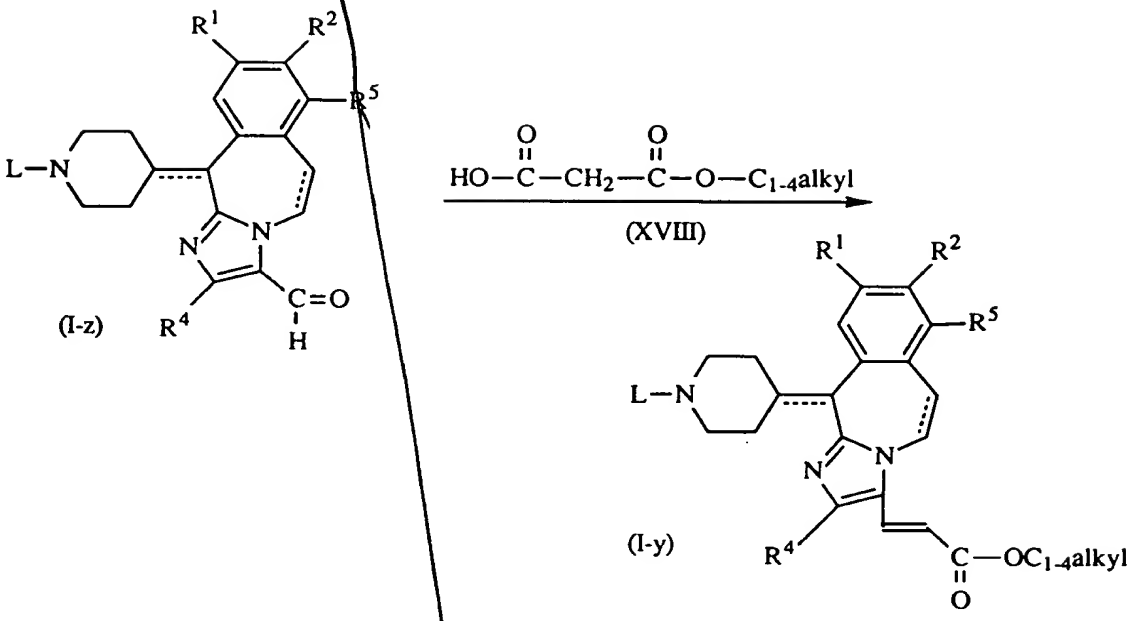
w) formylating a compound of formula (I-u) in a reaction-inert solvent yielding a compound of formula (I-w)



which optionally may be reduced in a reaction-inert solvent in the presence of a reductant yielding an alcohol of formula (I-x)

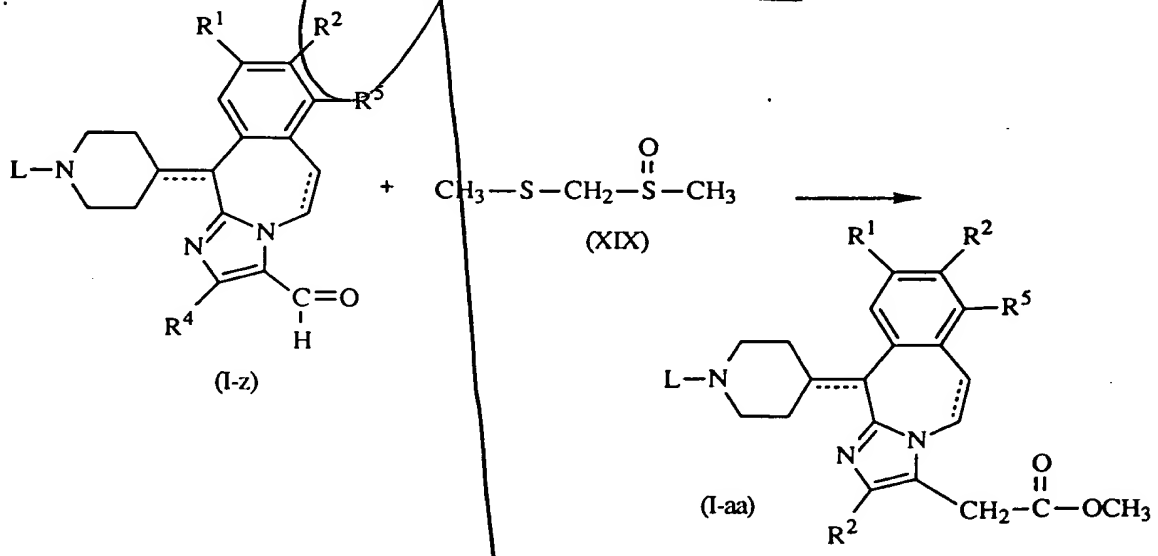


x) reacting a compound of formula (I-z) with a reagent of formula (XVIII) in the presence of a base yielding a compound of formula (I-y)



which optionally may be hydrolyzed in the presence of an acid or a base yielding the corresponding hydroxycarbonyl compound;

y) reacting a compound of formula (I-z) with a reagent of formula (XIX) in the presence of benzyl trimethyl ammonium hydroxide in a reaction-inert solvent yielding a compound of formula (I-aa)



which optionally can be hydrolyzed in the presence of an acid or a base into the corresponding hydroxycarbonyl compound;

and, if desired, convering the compounds of formula (I) into each other following art-known functional group transformation reactions, and further, if desired,

converting the compounds of formula (I) into a therapeutically active non-toxic addition salt form by treatment with an acid or a base; or conversely, converting the salt into the free base or acid with alkali, respectively acid; and/or preparing stereochemically isomeric forms thereof.

add a2

add b1

add b2